IFW 1639

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*ADMITTED IN NEW JERSEY ONLY
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September 22, 2004

VIA PRIORITY MAIL
Alan Koller, Ph.D., Esq.
Sr. Assistant General Counsel
Purdue Pharma LP
One Stamford Forum
Stamford, CT 06901

Re: U.S. Patent Application No. 10/056,475
Entitled: **ANALGESIC COMBINATION OF OXYCODONE AND 6-METHOXY-2-NAPHTHYLACETIC ACID**
Euro-Celtique, S.A.
Purdue Ref. No.: PT0176
Our Ref. No.: 200.1079CON3

Dear Alan:

We have now received an Office Action for the above-referenced patent application, a copy of which along with related papers are enclosed for your review.

A response to the Office Action is due **December 7, 2004**, although extensions of time are obtainable if necessary.

Absent your instructions to the contrary, we shall prepare a draft response for your review and consideration prior to the due date. On the other hand, if you have any comments or suggestions concerning this Office Action, we look forward to receiving the same.

Very truly yours,

Clifford M. Davidson

CMD:ie
Enclosure

cc: Robert J. Paradiso, Esq.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/056,475	01/25/2002	Ronald M. Burch	200.1079CON3	5119

7590 09/07/2004

Davidson, Davidson & Kappel, LLC
14th Floor
485 Seventh Avenue
New York, NY 10018

EXAMINER	
CELSA, BENNETT M	
ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 09/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Excel 9-10-04
IPM 9-10-04

3-7-05 Office Action Response Due (Deadline Date)
12-7-04 Office Action Response Due (3 month Date)
11-7-04 Reminder
10-7-04 send reporting letter

CMO/RJP/RVZ

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	10/056,475	BURCH ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-43 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-43 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/2/02;1/25/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 37-43 and 45 are currently pending and under consideration..

Election/Restriction

1. Applicant's election without traverse of Group II (claims 37-43 and 45 methods of treating pain using oxycodone and 6-methoxy-2-naphythylacetic acid or 6-MNA in the correspondence dated 6/14/04 is acknowledged.

Priority

Applicant should update the cross-reference to parent application which has subsequently issued as a patent.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 37-40, 42-43 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. US Pat. No. 4,569,937 (2/86) and Richardson et al. Drug Safety (Oct. 1996) Vol. 15(4) pages 249-260.

Baker et al. teach pharmaceutical compositions for relieving pain in humans or mammals (e.g. mice, rats etc.) comprising a combination of :

a. a narcotic analgesic (preferably oxycodone: see formulations col. 4-8; mice data in col. 8-10; patent claims), or a pharmaceutically acceptable salt thereof; and

b. a non-steroidal anti-inflammatory drug or NSAID (preferably ibuprofen: see col. 1-2), or a pharmaceutically acceptable suitable salt thereof,

in a weight ratio of about 1:800 (e.g. .001:1) to 1:1 (compare to present claim 47: See col. 2)

with oxycodone amounts of about 5 mgs-600mgs (compare to present claim 46).

The Baker reference teaches oral administration (e.g. see present claim 39), which can be coadministered in a "single dosage form" (e.g. see col. 3-8: and present claim 40) or sequentially administered (e.g. as in present claim 42; see i.e. col. 8-9 ; ".. mice are dosed sequentially..."). The Baker et al. reference teach that dose ratios can be adjusted and that the analgesic activity of the combined oxycodone and ibuprofen activity is "unexpectedly enhanced" or synergistic "i.e. the resulting activity is greater than the activity expected from the sum of the activities of the individual components", thereby permitting "reduced dosages of narcotic analgesics" (e.g. oxycodone) AND

which diminishes adverse side effects (e.g. addiction) and toxicity which would result from the otherwise required amounts of the individual drug components" resulting from high dosages of oxycodone or NSAID's such as ibuprofen. See e.g. col. 1-2; col. 3, lines 19-32 (e.g. compare to present 43 and 44 "reduced" active ingredients). Accordingly, Baker would teach the use of therapeutic and subtherapeutic amounts of oxycodone and/or ibuprofen in view of the synergistic nature of the combinations and the desire to reduce the toxicity and/or side-effects of both agents; and as required by the doctor for his/her particular patient., including dosage optimization e.g. dosage overlapping of active ingredients. See e.g. col. 3 where dosage is modified to suit the particular patient.

The Baker analgesic composition differs from that presently claimed in that it fails to teach the substitution of nimesulide for ibuprofen, or alternatively, the further incorporation of (e.g. encompassed by "consisting essentially of") Nimesulide into the Baker compositions.

Richardson et al.. teach that 6-methoxy-2-naphythylacetic acid (or 6-MNA), the active metabolite of nabumetone, and like nabumetone and Ibuprofen, is more COX-2 than COX-1 selective and as such this non-steroidal anti-inflammatory drug (e.g. NSAID) is associated with a favourable adverse effect profile with low incidence of GI bleeding and low toxicity. E.g. see abstract, page 253 (table 1) and pages 255-256.

Accordingly, one of ordinary skill in the art would have been motivated to substitute 6-MNA (a NSAID) for ibuprofen (a different NSAID) in the Baker reference compositions in light of the Richardson et al. reference teaching that 6-MNA is as

efficacious, and safe, with few side effects (e.g. as compared to other less selective COX-2 inhibitor NSAID's including ibuprofen).

Alternatively, one of ordinary skill in the art would have been motivated to incorporate 6-MNA, with its potent analgesia and reduced side-effect, into the Baker ibuprofen/oxycodone compositions in order to reduce the amounts (e.g. therapeutic/subtherapeutic) of ibuprofen/oxycodone in order to further avoid the side effects (e.g addiction) or toxicity resulting from ibuprofen/oxycodone.

Additionally, it is noted that the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two (or more) compositions each of which is taught by the prior art to be useful for the same purpose

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Baker reference analgesic composition by substituting the NSAID Nimesulide (for the NSAID ibuprofen) or supplement Baker's composition with 6-MNA in light of the benefits of 6-MNA increased safety/decreased side effect as compared to other NSAID's as taught by the Richardson et al. reference.

4. Claims 37-43 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Baker et al. '937 and Richardson et al. applied to claims 37-40, 42-43 and 45 above, and further in view of Mayer et al. US Pat. No. 5834,479 (11/98).

The teaching of the Baker and Richardson et al. references recited above is hereby incorporated by reference in its entirety.

To the extent that the Baker and Richardson et al. references fail to teach the administration of the analgesia active agent (e.g. 6-MNA) "before, ... with, or after" administration of the oxycodone" (particularly before/after) (e.g. see present claim 41) the Mayer et al. reference is cited.

The Mayer et al. reference teaches that analgesia effectiveness of an analgesia active agent (e.g. a NSAID, such as ibuprofen see i.e. table in col. 7) can be "significantly enhanced" by administering (e.g. oral administration) the active agent "prior to, with or following the administration of an analgesia enhancer" (e.g. a nontoxic NMDA receptor blocker and/or a nontoxic substance that blocks at least one major intracellular consequence of NMDA receptor activation) such as "dextromethorphan", which is the D-isomer of codeine . See e.g. col. 1; patent claims.

Accordingly, the Mayer et al. reference provides motivation to one of ordinary skill in the art to not only co- administer different analgesic agents to achieve enhanced analgesia, but to also administer the NSAID prior or subsequent to the second analgesic agent i.e. an analgesia enhancer, which includes codeine or its derivatives (e.g. dextromethorphan, dextrorphan, oxycodone etc.) .

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the combined Baker and Richardson et al. reference teachings by administering one of the analgesic active agents (e.g. 6-MNA) "before, ... with, or after" administration of the second analgesic agent (e.g. oxycodone) in order to obtain significantly enhanced analgesia.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
August 26, 2004

FORM PTO-1449
(REV. 7-80)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

LIST OF PRIOR ART CITED BY APPLICANT

(Use several sheets if necessary)

ATTY. DOCKET NO.: 200.1079CON3

SERIAL NO.: Not yet known 10/056,475

APPLICANT(S): Ronald M. BURCH, et al.

FILING DATE: Herewith

GROUP: Not Yet Known 1639

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	5 8 5 9 2 5 7	01/12/99	Talley	548	247	08/14/96
	AB	5 8 6 3 9 2 2	01/26/99	Mayer, et al.	514	270	07/02/99
	AC	5 8 4 0 7 3 1	11/24/98	Mayer, et al.	514	289	08/02/95
	AD	5 8 6 9 4 9 8	02/09/99	Mayer, et al.	514	282	07/07/97
	AE	5 8 6 1 4 1 9	01/19/99	Dube, et al.	514	334	07/11/97
	AF	5 7 8 9 4 1 3	08/04/98	Black, et al.	514	255	01/21/97
	AG	5 6 0 4 2 6 0	02/18/97	Guay, et al.	514	605	11/04/93
	AH	5 4 5 8 8 7 9	10/17/95	Singh, et al.	424	400	09/30/94
	AI	5 5 1 6 8 0 3	05/14/96	Raffa	514	570	03/01/95
	AJ	5 8 4 3 4 6 8	12/01/98	Burkoth, et al.	424	448	05/13/96

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	AK	Differential Inhibition of Cyclooxygenase-1 (COX-1) and -2 (COX) By NSAIDS: Consequences on Anti-Inflammatory Activity Versus Gastric and Renal Safety, M. Peiret, et al., Inflammopharmacology 4: 61-70, (1996).
	AL	Differential effects of inhibitors of cyclooxygenase (cyclooxygenase 1 and cyclooxygenase 2) in acute inflammation, Derek W. Gilroy, et al. European J. Pharm 355 pp 211-217, (1998).
	AM	Cyclooxygenases 1 and 2, J.R. Vane, et al. Annu. Rev. Pharmacol. Toxicol. 38: 97-121, (1998).
	AN	Analysis of the effects of cyclooxygenase (COX)-1 and COX-2 in spinal nociceptive transmission using indomethacin, a non-selective COX inhibitor, and NS-398, a COX-2 selective inhibitor, Tatsuo Yamamoto, et al. Brain Research 739:104-110, (1996)
	AO	Comparative Analgesic Efficacy of Nimesulide and Diclofenac Gels after Topical Application on the Skin, S. Sengupta, et al., Skin Pharmacol. And Applied Skin Phys. 11:273-278, (1998).
	AP	Carrageenan-induced hyperalgesia is associated with increased cyclo-oxygenase-2 expression in spinal cord, Cartiona Hay and Jacqueline de Belleroche, Neuro Report 8, 1249-1251, (1997).
	AQ	The Mechanisms of Action of NSAIDs in Analgesia, Jeremy N. Cashman, Drugs 52 Supp. 5:13-23, (1996).
	AR	Differential effects of inhibition of isoforms of cyclooxygenase (COX-1, COX-2) in chronic inflammation, D.W. Gilroy, et al. Inflamm. Res. 47:79-85, (1998).
	AS	Constitutive Cyclooxygenase (COX-1) and Inducible Cyclooxygenase (COX-2): Rationale for Selective Inhibition and Progress to Date, Don E. Griswold and Jerry L. Adams, Medicinal Research Reviews, Vol. 16, No. 2, pp. 181-206, (1996).

EXAMINER

DATE CONSIDERED 9/26/04

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: 200.1079CON3	SERIAL NO.: Not Yet Known 10/056,475
LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary)		APPLICANT(S): Ronald M. BURCH, et al.	
		FILING DATE: Not Yet Known	GROUP: Not Yet Known 1639

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	BA						
	BB						
	BC						
	BD						
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	BJ						
	BK						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	BL							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	BM	Cyclooxygenase in biology and disease, Raymond N. Dubois, et al., FASEB J. Vol. 12 pp. 1063-1073 (1998).
	BN	Pharmacology of Meloxicam, A new Non-Steroidal Anti-Inflammatory Drug With An Improved Safety Profile Through Preferential Inhibition of COX-2, G. Engelhardt, British J. Rheumatology, 35 (supp 1):4-12, (1996)
	BO	Cyclooxygenase 1 Contributes to Inflammatory Responses in Rats and Mice: Implications for Gastrointestinal Toxicity, John L. Wallace, et al. Gastroenterology, 115:101-109 (1998).
	BP	Distinct isoforms (COX-1 and COX-2) of cyclooxygenase: possible physiological and therapeutic implications, M. Pairet and G. Engelhardt, Fundam. Clin. Pharmacol. 10:1-15, (1996).
	BQ	Involvement of Prostaglandins Produced by Cyclooxygenase-1 in Murine Viscernonociception Induced by Phenylquinone, Hidenobu Kusuhara, et al. Prostaglandins 55: 43-49, (1998).
	BR	Effect of COX-1 and COX-2 Inhibition on Induction and Maintenance of Carrageenan-Evoked Thermal Hyperalgesia in Rats, D. Dirig, et al. J. Pharmacol. And Experimental Therapeutics Vol. 285, No. 3, pp 1031-1038.

EXAMINER	DATE CONSIDERED
	8/5/04

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FORM PTO-1449 (REV. 7-80)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.: 200.1079CON3	SERIAL NO.: Not Yet Knownd 10/056,475
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	CA						
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	CC						
	CD						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	CE	9 9 0 7 4 1 3	2/18/99	WO				
	CF	9 9 3 2 1 1 9	7/1/99	WO				
	CG							
	CH							
	CI							
	CJ							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	CK	Effect of meloxicam on postoperative pain after abdominal hysterectomy, J.P. Thompson et al. British Journal of Anaesthesia 84 (2) 151-4 (2000).
	CL	Intrathecal cyclooxygenase inhibitor administration attenuates morphine antinociceptive tolerance in rats. C.S. Wong et al., British Journal of Anaesthesia 85 (5) 747-51 (2000).
	CM	Cyclooxygenase inhibitors increase morphine effects on mesolimbic dopamine neurons, M. Melis, et al. Eur. J. Pharmacology 387 (1) R1-R3 (2000).
	CN	Synergistic antiallodynic effects of spinal morphine with ketorolac and selective COX-1 and COX -2 inhibitors in nerve-injured rats, J.M. Lashbrook, et al. Pain 82 (1) 65-72 (1999).
	CO	Enhancement of opioid inhibition of gaba-ergic synaptic transmission by cyclo-oxygenase inhibitors in rat periaqueductal grey neurones, Vaughn et al. British Journal of Pharmacology 123 (8) 1479-81 (1998).

EXAMINER	DATE CONSIDERED
	8/26/04

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		FILING DATE: Not Yet Known	GROUP: Not Yet Known 1639

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	DA	5 4 7 4 9 9 5	12/12/95	Ducharme et al.	514	241	01/10/94
	DB	5 6 9 1 3 7 4	11/25/97	Black et al.	514	473	05/18/95
	DC						
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FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	DL							
	DM							
	DN							
	DO							
	DP							

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	DQ	
	DR	
	DS	

EXAMINER	DATE CONSIDERED
	8/20/04

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FORM PTO-1449 (REV. 7-80)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

LIST OF PRIOR ART CITED BY APPLICANT

(Use several sheets if necessary)

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APPLICANT(S): Ronald M. BURCH, et al.

FILING DATE: Not Yet Known

GROUP: Not Yet Known 1639

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	EA	3 8 0 0 0 4 1	03/26/74	Miller, et al.	424	273	03/02/71
	EB	4 3 2 2 4 2 7	03/30/82	Buyinski, et al.	424	260	04/16/81
	EC	4 3 3 8 3 2 4	06/06/82	Gardocki	424	268	03/17/81
	ED	4 4 0 4 2 1 0	09/13/83	Schmidt	424	260	06/30/82
	EE	4 4 0 7 8 0 4	10/04/83	Schmidt	424	260	06/30/82
	EF	4 4 0 7 8 0 5	10/04/83	Schmidt	424	260	08/30/82
	EG	4 4 6 4 3 7 6	08/07/84	Sunshine, et al.	424	253	10/11/83
	EH	4 4 8 6 4 3 6	12/04/84	Sunshine, et al.	424	253	03/11/83
	EI	4 4 8 9 0 8 0	12/18/84	Lomen	424	260	12/06/82

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	EJ	2 0 2 3 3 4 9	02/18/91	Canada	A61K	31/44		
	EK	0 2 7 4 8 4 5	07/20/88	EP (A1)	A61K	31/19		
	EL	0 3 8 8 1 2 5	09/19/90	EP (A1)	A61K	31/485		

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	EM	Pharmacokinetics and Drug Input Characteristics for a Diclofenac-Codeine Phosphate Combination Following Oral and Rectal Administration A. Hansen, et al. Arzneim-Forsch./Drug Res. 46 (I) 57-63 (1996).
	EN	Comparison of a Standard Ibuprofen Treatment Regimen with a New Ibuprofen/Paracetamol/Codeine Combination in Chronic Osteo-arthritis G.K. Vlok, et al. Univ. Stellenbosch and Tygerberg Hospital, Dept. Orthopaedic Surg. pp 3-6, (1987).
	EO	
	EP	
	EQ	
	ER	

EXAMINER

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The Clinical Implications of Inhibition of the Inducible Form of Cyclo-Oxygenase

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Summary

There are 2 isoenzymes of cyclo-oxygenase (COX). There is a constitutive enzyme COX-1 which has a wide tissue distribution. In addition there is an inducible enzyme COX-2 which has a restricted tissue distribution. The inducible enzyme COX-2 is responsible for the generation of prostaglandins at sites of tissue inflammation and its inhibition is associated with an anti-inflammatory action. The constitutive enzyme, COX-1 is responsible for the production of prostaglandins with multiple functions. One well known and clinically important function is the gastroprotective effect of the prostaglandins produced in the gastric mucosa. While selective COX-2 inhibition may be associated with a reduced incidence of gastric adverse effects, a concern remains that its inhibition at other locations may be associated with other adverse effects.

Inflammation is the body's response to tissue damage. The major purpose of this immensely complex response is to permit the entry of fluid, proteins and cells from the bloodstream into the damaged tissues to produce tissue healing. The major features of inflammation are: vasodilatation, increased vascular permeability and cellular infiltration. The net effect is an increased blood supply and entry of proteins and cells into the affected site. In clinical practice this produces pain, swelling and erythema. One of the major groups of chemical mediators involved in the inflammatory response is the prostaglandins, which are synthesised by the enzyme cyclo-oxygenase (COX) from arachidonic acid.[1] It is now apparent that there are 2 isoenzymes of COX, a constitutive enzyme COX-1 responsible for the production of prostaglandins with 'general housekeeping' functions in the body, such as maintenance of renal perfusion and a protective effect in the gastric mucosa against ulceration, and an inducible enzyme COX-2 responsible for the production of the pro-inflammatory prostaglandins. The nonsteroidal anti-inflammatory drugs (NSAIDs), by inhibiting the COX enzyme, are able to reduce the pain and swelling of inflammation. In theory, if new molecules that preferentially inhibit the inducible enzyme alone could be developed then these would have an anti-inflammatory effect and would not affect the production of prostaglandins for general 'housekeeping functions'. In this article we will review the clinical experience of COX selectivity as a determinant of NSAID toxicity.

1. Prostaglandin Metabolism

The prostaglandins are a family of lipid soluble molecules synthesised by the COX enzyme from arachidonic acid, a 20 carbon unsaturated fatty acid.[2] There are at least 16 different prostaglandins and these can be divided into 9 chemical

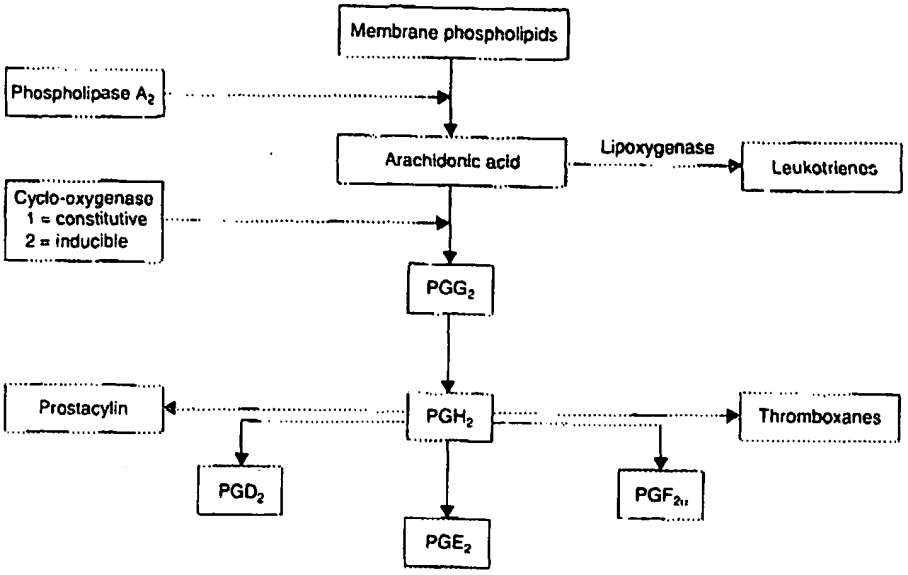

Fig.1. The pathways of prostaglandin biosynthesis. *Abbreviation*: PG = prostaglandin.

classes. The prostaglandins do not exist free in the tissues but are synthesised and released in response to the appropriate stimulus. Their biosynthetic pathways are illustrated in figure 1. Prostaglandins are found in many human tissues and have a diverse range of effects.

For immunoregulation prostaglandin (PG) E_2 has been most extensively studied and has both pro-inflammatory and anti-inflammatory roles. It is found in high levels in acutely inflamed tissue where it is responsible for vasodilatation[3] and sensitises nerve endings to bradykinin and histamine, resulting in the pain characteristic of inflammation (i.e. pro-inflammatory action).[4] In chronic inflammation PGE_2, again produced by COX-2,[5] has an anti-inflammatory action and suppresses a wide variety of cellular functions including lymphocyte proliferation, T cell cytotoxicity and leucocyte motility. A further important role of PGE_2 [and prostacyclin (PGI_2)] is as a vasodilator to maintain renal perfusion; this is of particular importance at times of circulatory collapse.[6] PGI_2 has a lesser role in inflammation but a major one as a gastroprotective agent.[7]

In addition, prostaglandins have an important role in haemostasis and inhibition of their production results in a bleeding tendency.[8] Therefore the blanket inhibition of COX activity by NSAIDs results in an anti-inflammatory action, a tendency to peptic ulceration and renal toxicity.

It is now clear that there are 2 isoenzymes of COX: there is a constitutive enzyme (COX-1) with a wide tissue distribution and an inducible enzyme (COX-2).[9-11] The constitutive enzyme (COX-1) is responsible for the production of prostaglandins with general (i.e. continuously required) 'housekeeping' functions.[9] By contrast, the inducible enzyme has a limited constitutive expression, but is generated in many tissues as a response to an external stimulus. The range of prostaglandins produced by COX-1 and 2 are similar, their physiological role being dependent on their tissue of origin and the stimulus determining their production. For example PGE_2 is synthesised by:

- COX-1 in the gastric mucosa and has a protective effect against the development of mucosal ulceration;

- COX-1 and COX-2 in the renal mesangium and has a role in renal haemostasis and salt balance;
- COX-2 at sites of both acute and chronic tissue inflammation and contributes to pain and vasodilatation.

The identification of COX-2 has produced interest in the development of molecules which preferentially inhibit this inducible isoenzyme alone. In theory such a molecule would have an (improved) anti-inflammatory effect with an improved safety profile.[12] However, as stated above it is now becoming increasingly recognised that prostaglandins produced by COX-2 have many other important physiological roles in addition to their pro-inflammatory effect. For example COX-2 has been demonstrated to be responsible for the production of prostaglandins in the kidney, brain, seminal vesicle and uterus, and clearly inhibition of their synthesis at these sites may not be desirable.

2. Isoenzymes of Cyclo-Oxygenase (COX)

The 2 isoenzymes of COX have 60% amino acid homology and both metabolise arachidonic acid to make prostaglandins. They have similar binding sites (and binding constants) for arachidonic acid but there are important differences in structure and function: COX-1 has a greater specificity for $C_{20:4}$ fatty acids, whereas COX-2 can use 18 or 20 carbon acids equally well and is therefore able to accept a wider range of substrate.[13] The isoenzymes are coded for by different genes. The COX-2 gene is larger and codes for 4kb of mRNA, the smaller COX-1 gene codes for 2.8kb of mRNA.[9,11,14] Furthermore, expression of the COX-2 gene (but not COX-1) can be modulated by the binding of glucocorticoids,[10] interleukin-1, interleukin-6 and phorbol esters.[15,16] Therefore the synthesis of COX-2 gene is responsive to a pro-inflammatory stimulus. The clinical implication of COX-2 inhibition can only be understood with a knowledge of the biological effects of prostaglandins produced by this enzyme.

3. Biological Effects of Prostaglandins

3.1 Role in the Gastric Mucosa

In the gastric mucosa the following physiological roles have been identified for the prostaglandins generated by COX-1 (see reference 17) for a review of this topic):

- Inhibition of basal cell gastric acid production.
- Stimulation of basal cell bicarbonate secretion.
- Stimulation of basal cell gastric mucus secretion. The increase in mucus thickness increases the pH gradient between the lumen and the epithelial surface.
- Enhanced gastric blood flow during acid production, thus preventing the development of erosions that occur when such vasodilatation does not occur.
- Stimulation of rapid repair of disrupted epithelium. This may involve migration of basal cells toward the lumen to repair mucosal injury and enhanced RNA and protein synthesis.

3.2 Role in Haemostasis

The enzyme thromboxane synthetase is responsible for the production of thromboxane within platelets, while COX is responsible for the production of PGI_2 in the vascular endothelium. Thromboxane stimulates platelet aggregation which is inhibited by PGI_2. NSAIDs inhibit both COX and thromboxane synthetase and decrease the production of PGI_2 and thromboxane respectively. It is the balance of inhibition of these 2 enzymes that determines the overall effect a given NSAID has on haemostasis.[8] Since the vascular endothelium is capable of synthesising more COX but platelets are not able to synthesise more thromboxane synthetase, treatment with NSAIDs tends to result in a relative increase in PGI_2 levels and a bleeding tendency.

The human endothelium possesses both the constitutive COX-1 and the inducible isoenzyme COX-2.[18] Interleukin-1 and 6 have been demonstrated to regulate the transcription of the COX-2 gene in the endothelium.[18,19] In addition, activation

of the gene for COX-2 represents an early response of the vascular smooth muscle to injury. Platelet derived growth factor, epidermal growth factor and thrombin are strong inducers whilst interleukin-1α and acidic and basic fibroblast growth factors are weak inducers.[20]

3.3 Role in Tissue Inflammation

Under normal conditions resting neutrophils, macrophages and fibroblasts show little or no COX activity and hence prostaglandin production.[5] However in response to an inflammatory stimulus (e.g. pro-inflammatory cytokines, bacterial lipopolysaccharide and growth factors) there is increased COX activity due to new gene expression of COX-2. Furthermore fibroblasts and endothelial cells from human rheumatoid synovial tissue synthesise increased amounts of COX-2 in response to stimulation by interleukin-1 and phorbol esters. Glucocorticoids and possibly some NSAIDs can inhibit these effects on COX-2 production.[15,16]

3.4 Role in Renal Function

It is widely accepted that renal prostaglandins play an important role in the maintenance of renal haemostasis and tubular function. The effects of prostaglandins on the kidney may be summarised as follows.

- Maintenance of normal renal blood flow. PGE_2, $PGF_{2\alpha}$ and PGI_2 are all potent vasodilators.
- Decreased renal response to antidiuretic hormone (ADH). Prostaglandins inhibit the effect of ADH on the collecting duct.
- Decreased resorption of sodium and chloride from the ascending limb of the loop of Henle in response to PGE_2.
- Increased renin release. PGE_2 and PGI_2 stimulate the release of renin from the juxtaglomerular apparatus.

It is becoming increasingly recognised that the maintenance of normal renal haemostasis is dependant on the ability to generate prostaglandins in response to an appropriate stimulus. *In vitro* studies have demonstrated that continuous stretching of rat glomerular mesangial cells results in cell proliferation, protein synthesis and the generation of prostaglandins by COX-2.[21] The ability to respond to mechanical stress by the production of vasoactive prostaglandins is thought to be important in renal homeostasis.

Cyclosporin, an immunosuppressive drug with considerable renal toxicity, inhibits the synthesis of COX-2 in rat renal mesangial cells in response to pro-inflammatory cytokines. This may contribute to its nephrotoxicity.[22]

3.5 Role in Brain Signalling

Prostaglandins have been identified as important neurotransmitters in the brain. Animal experimentation has shown that the COX-2 isoenzyme is widely distributed throughout the forebrain in discrete populations of neurons and is enriched in the cortex and hippocampus.[23] Basal expression of COX-2 appears to be regulated by background synaptic activity and can rapidly and transiently induce increased synaptic activity or seizures.[23,24] It is likely that COX-2 induction is an important factor in the regulation of cerebral prostaglandin synaptic transmission.

3.6 Role in Skeletal Muscle

It has been reported that differentiated skeletal muscle in tissue culture developed a 3-fold increase in COX-2 activity and anabolic myofibre growth in response to repetitive mechanical stimulation. The inhibition of COX-2 expression prevented the muscle fibre growth. The obvious conclusion made was that muscle cell growth was at least in part dependent on COX-2 induction.[25]

3.7 Role in the Uterus

Prostaglandins are required for normal uterine function. It has been postulated that the induction COX-2 by uterine stromal cells may be required to support the prostaglandin production necessary for the early stages of embryo implantation.[26] In addition, the induction of COX-2 probably mediates the increase in prostaglandin synthesis occurring

within the amniotic membranes of the placenta that occurs at the onset of labour.[127]

3.8 Role of COX in the Seminal Vesicle

COX-2 was originally described in the seminal vesicle. It has a role in the production of prostaglandins present in semen.[128]

4. Clinical Significance of COX-2 Inhibition

In addressing the clinical significance of COX-2 inhibition there are 2 questions to be answered. Is selective inhibition of COX-2 associated with a decreased incidence of adverse effects and does selective COX-2 inhibition create its own adverse effects?

4.1 COX Selectivity of the Currently Available NSAIDs

In assessing the clinical implications of COX-2 inhibition it is useful first to consider the NSAIDs currently available on the market and determine to what extent their COX selectivity influences their adverse effect profile. The ability of different NSAIDs to inhibit the 2 isoenzymes of COX has been investigated using a number of biological assays.[126,29-31] The ability of a molecule to inhibit COX is determined in terms of its IC_{50}, the concentration of the compound required to inhibit 50% of COX activity. To compare the activity of NSAIDs on COX-1 and COX-2 the ratio of the IC_{50} of COX-2 : COX-1 is employed. The lower the ratio, the greater the specificity for COX-2 i.e. a ratio of >1 indicates that a given compound has more activity on COX-2 than COX-1. It should be noted that the different values for COX ratios given by different investigators are due to the use of different COX preparations and that no preparation has been accepted as a 'gold standard'. The results are summarised in table I. These biological assays demonstrate clear cut differences in the ability of NSAIDs to inhibit the 2 isoenzymes. In the following section the COX selectivity of NSAIDs is compared to their adverse effect profiles.

4.2 Clinical Experience of Toxicity with Established NSAIDs

The most troublesome adverse effect associated with NSAID usage is gastrointestinal toxicity and it is this adverse effect that will be discussed in greatest detail.

Langman et al.[132] compared the use of NSAIDs in 1144 patients aged ≥60 years admitted to hospital with bleeding peptic ulcer with age- and gender-matched hospital and community controls. They

Table I. Comparison of the cyclo-oxygenase (COX) selectivity of NSAIDs with the reported incidence (odds ratio) of upper gastrointestinal bleeding derived from 2 large case controlled studies[32,33] and their toxicity index[34]

NSAID	Odds ratio[32]	Odds ratio[33]	Toxicity index[34]	COX-2:COX-1[47]	COX-2:COX-1 [34]	COX-2:COX-1[31]
Azapropazone	31.5 (10.3-96.9)	23.4 (6.9-79.5)				
Ketoprofen	23.7 (7.6-74.2)	5.4 (2.6-11.3)	4.69			4.6
Piroxicam	3.7 (7.1-26.3)	18 (8.2-39.6)	3.96	33	9.54	
Indomethacin	11.3 (6.3-20.3)	6.3 (3.3-12.2)	5.15	107	22.3	14.7
Naproxen	9.1 (5.5-15.1)	3.1 (1.7-5.9)	3.01			3.3
Diclofenac	4.2 (2.6 -6.8)		4.48	2.2		1.6
Ibuprofen	2.0 (1.4-2.8)	2.9 (1.7-5)	2.68		0.67	0.6
Tenoxicam				15		
Meloxicam				0.33		
Aspirin (acetylsalicylic acid)			1.77			
6-Methoxy-2-naphthylacetic acid[a]					0.14	0.3

a 6-Methoxy-2-naphthylacetic acid is the active metabolite of nabumetone.

found that peptic ulcer bleeding was strongly associated with the use of NSAIDs in the 3 months prior to admission. For the most commonly used NSAIDs it was possible to calculate an odds ratio for bleeding (table I). Those NSAIDs with the least favourable odds ratios were azapropazone and ketoprofen, an intermediate ratio was seen for indomethacin, naproxen and piroxicam and the most favourable ratio was seen for ibuprofen and diclofenac. The authors noted that the risk of gastrointestinal bleeding for most NSAIDs tended to be greatest in those who had only recently started treatment. These patients were more likely to be on the full recommended dose than those who had been taking an NSAID long term.

Using a different approach to determine the risk of upper gastrointestinal bleeding with NSAID therapy, Garcia Rodriguez and Jick[133] identified 1457 cases of upper gastrointestinal bleeding from the records of general practitioners and calculated the odds ratios for gastrointestinal bleeding using appropriate controls (table I). In general terms, the results give similar odds ratios for all gastrointestinal adverse effects.

A further measure of NSAID toxicity can be obtained from the ARAMIS (Arthritis, Rheumatism and Aging Medical Information System) database. The ARAMIS database contains detailed clinical information on more than 23 000 patients with rheumatic disorders in the US and Canada. The ARAMIS Post-Marketing Surveillance Program (PMS) has prospectively followed outcome status and drug adverse effects in a cohort of 2976 consecutively enrolled patients with rheumatoid arthritis giving 27 936 patient years of observation. Using the information obtained from this database Singh et al.[134] have developed a 'toxicity index' to give an overall measure of the adverse effect profile of different NSAIDs (and disease modifying agents which are not considered here).[134,135] The components of the index include adverse clinical symptoms, laboratory abnormalities and hospital admissions. Each adverse effect is weighted for severity based on the physician judgement. For each drug considered, the higher the toxicity index the greater the drug toxicity (table I). These 3 studies have provided an enormous amount of information about relative NSAID toxicity and it is of great interest to relate this information to their known COX selectivities.

The results of Langman et al.[132] and Garcia Rodriguez and Jick[133] are in reasonable agreement; both studies demonstrate that azapropazone, piroxicam and indomethacin have the highest odds ratios for gastrointestinal bleeding. The only major difference in the results of these 2 studies was for ketoprofen, which had a far less favourable odds ratio in the study of Langman et al.[132] compared with the odds ration obtained by Garcia Rodriguez and Jick.[133]

Direct comparison between the odds ratios found in the studies of Langman et al.[132] and Garcia Rodriguez and Jick[133] with the toxicity index scores of Singh et al.[134] is difficult because this latter measure takes into account all adverse effects, not simply the incidence of gastrointestinal bleeding. Having said this, it can be seen that indomethacin and ketoprofen (according to the results of Langman et al.[132]) have both a high toxicity index and odds ratio for gastrointestinal bleeding. By contrast ibuprofen has a low toxicity index and odds ratio. A further point to note is the lower toxicity index associated with aspirin (acetylsalicylic acid) use than might have been expected when compared to the odds ratio.

The results of *in vitro* experiments for a particular NSAID cannot be directly translated into the clinical situation because of the differences in pharmacokinetic parameters to which the NSAID would be subjected. However, comparison of COX selectivities with adverse effects raises a number of points of interest.

- The COX selectivity of an individual NSAID is dependent on the biological assay used for its measurement. This means that the results of studies using different assays are not identical, but nevertheless the results do show a reasonable degree of agreement.
- The COX-1 selective drugs indomethacin and piroxicam are associated with an increased in-

cidence of gastrointestinal bleeding and high toxicity indices.

- Ibuprofen is more selective for COX-2 than COX-1 and is associated with a low incidence of gastrointestinal bleeding and low toxicity index.
- 6-Methoxy-2-naphthylacetic acid (6-MNA, the active metabolite of nabumetone) is more COX-2 than COX-1 selective. This NSAID is associated with a favourable adverse effect profile and this discussed further in section 5.1.
- Aspirin is the most COX-1 selective of the drugs tested and has a low toxicity index. This indicates that other factors are important in determining toxicity.
- Meloxicam is predominantly COX-2 selective. This new drug is discussed further in section 5.3.
- The COX selectivity of NSAIDs *may* be an indicator of the likelihood of adverse effects but the absolute concentration of NSAID required to inhibit COX is likely to be important also.

In summary the results of these clinical studies demonstrate convincingly that the incidence of gastrointestinal adverse effects varies widely between the currently available NSAIDs. COX-2 selectivity appears to be associated with a decreased incidence of gastrointestinal adverse effects.

5. New Developments in NSAID Therapy

There have been a number of new NSAIDs recently introduced onto the market which demonstrate favourable adverse effect profiles. It is interesting to investigate to what extent COX selectivity accounts for these properties.

5.1 Nabumetone

Nabumetone is a nonacidic NSAID that is established for the treatment of rheumatoid arthritis and osteoarthritis. Nabumetone can be distinguished from other NSAIDs by its excellent adverse effect profile.[136] Nabumetone has a number of interesting pharmacological properties which collectively result in a reduced incidence of adverse effects.[137]

In vitro experimental work (see table I) demonstrates that the active metabolite of nabumetone, 6-MNA, is COX-2 selective and this is likely to contribute to its favourable adverse effect profile.[131] Indeed using a human COX enzyme system Barnett et al.[131] found nabumetone to be approximately 3.5 times more active against COX-2 than COX-1. Nabumetone is nonacidic and not subject to anion trapping in the gastric mucosa, and it is a prodrug and as such the active drug does not come into direct with the gastric mucosa.

Nabumetone has been evaluated in clinical trials involving more than 7400 patients and post market surveillance data exists for more than 37 000 patients.[138] The cumulative incidence of nabumetone-induced gastric perforations, ulcers and haemorrhage lies between 0.3 and 0.95% and overall the withdrawal rate due to adverse effects lies between 3 and 13%.[138] Initial clinical studies involved more than 7000 patients in a number of double blind comparative drug trials (comparator drugs used were placebo, naproxen and aspirin), and during these trials, only 10 patients were admitted to hospital for reasons thought to be linked to nabumetone therapy.[139-141] Of these 10 patients, 6 had gastritis, 1 had abdominal pain, 1 had a gastric ulcer, 1 had biliary colic and 1 had a diffuse rash due to candidiasis.

In premarketing studies in the US, 930 patients were involved in double blind comparative trials (comparator drugs were placebo, naproxen and aspirin). Of these only 7 patients had evidence of gastrointestinal bleeding: 4 had a positive result to a guaiac test; 1 had a gastric ulcer; and 2 had bloody or black stools.[139-141]

When results from all the premarketing studies performed in the US are combined, data on nearly 2000 patients are available. From this data the cumulative incidence of peptic ulceration has been estimated to be 0.3% at 6 months (5 patients), 0.5% at 1 year (8 patients), 0.8% at 2 years (13 patients) and 0.95% at 8 years (16 patients). The average treatment duration before peptic ulcer development

was 24 months, a result that is not substantially different from the general population.

In the comparative short term studies, 1.4% of naproxen-treated patients developed an ulcer at 6 months.[38] The average time to ulcer development was 2.5 months. In these studies, the withdrawal rate during the first year of treatment was 13%. In a subsequent 8 year open label follow up evaluation the withdrawal rate was 3 to 6% for each subsequent year.[42]

In premarketing studies performed outside the US the overall withdrawal rate due to adverse events was 6%.[38] The most common adverse events were gastrointestinal (nausea, dyspepsia, diarrhoea, constipation and abdominal pain), skin rashes, headaches and dizziness). Bone marrow suppression, renal failure and severe dermatological or CNS conditions were not seen.

In a prospective postmarketing surveillance study performed in the UK, primary care physicians enrolled 10 800 patients who were being treated with nabumetone.[43] In addition, hospital physicians enrolled 2005 patients who had received other NSAIDs (ibuprofen, naproxen, diclofenac, piroxicam, ketoprofen, indomethacin or fenbufen) who acted as controls. NSAID therapy was being given to treat a number of musculoskeletal conditions. The patients in the nabumetone-treated group were followed up for 12 months and patients in the control group were only followed for 3 months.[43] During the study period there were 2 deaths in the nabumetone-treated group which may have been attributable to this therapy. One death was due to a gastric ulcer and the other secondary to renal failure in a patient known to have preexisting renal failure. The cumulative incidence of gastric perforations, ulcers and bleeds was 0.2% at 12 months. Renal insufficiency occurred in 9 patients (0.08%); in 2 patients the renal failure was reversible after cessation of therapy. Overall, the incidence of adverse events was similar between nabumetone and the comparator drugs, though the different lengths of follow-up need to be borne in mind. The subsequent withdrawal rate was approximately 10% in the nabumetone patients. The incidence of adverse effects increased when the nabumetone dosage was increased from 500 mg/day to 1 g/day daily. However, there was no further increase in adverse effect incidence when the dosage was increased further to 2 g/day.

In a postmarketing surveillance study conducted in Germany, follow-up data was obtained on 28 000 patients treated with nabumetone for 6 weeks.[37] During this short period there were no deaths attributable to nabumetone. Again the most common adverse effects were gastrointestinal. In total, 5 patients required hospital admission for gastrointestinal adverse effects (1 patient with a gastric ulcer, 1 with a duodenal ulcer, 2 with bleeding ulcers and 1 with an intestinal bleed).

In summary, the incidence of gastric perforations, ulcers or bleeds observed in nabumetone-treated patients who have taken part in premarketing and postmarketing studies has varied between 0.02 to 0.95%. This contrasts with the incidence of serious gastropathy associated with chronic usage of other NSAIDs of 2 to 4% per year.[44,45] The incidence of renal toxicity is also slight and nabumetone has demonstrated an adverse effect on renal function in less than 1% of patients.[46] These data thus demonstrate that nabumetone has a distinct tolerability advantage over other currently available NSAIDs.

5.2 Etodolac

The NSAID etodolac is established in the symptomatic treatment of rheumatoid arthritis and osteoarthritis (in the US it is licensed for the treatment of osteoarthritis alone). In clinical trials, etodolac has an efficacy equivalent to other NSAIDs, though the withdrawal rate due to gastrointestinal adverse effects has been less at 7%, which is considerably lower than the rates of 12 to 15% observed for aspirin and indomethacin.[47] In a study of patients with rheumatoid arthritis, treatment for 4 weeks with etodolac did not produce any significant change in gastric and duodenal prostaglandin levels obtained from biopsy specimens; significant changes were seen with the comparative drug

naproxen.[48] In animal studies etodolac has not been shown to deplete renal PGE_2, in contrast to aspirin, indomethacin and piroxicam.[49] These results suggest COX-2 selectivity, a finding supported by the results of *in vitro* experimentation.[50]

5.3 Meloxicam

Meloxicam is a new NSAID of the enolic class which includes piroxicam and tenoxicam. It has recently been launched for the treatment of rheumatoid arthritis and osteoarthritis in South Africa and is approved in France, Sweden and Switzerland. In table I it can be seen that meloxicam is a more potent inhibitor of COX-2 than COX-1.[28]

Meloxicam is given once daily at a dose of 7.5 to 15mg. At this dose the drug has linear pharmacokinetics and an elimination half-life of approximately 20 hours.[51] This short half-life (in contrast to piroxicam and tenoxicam with elimination half lives of 50 and 70 hours respectively) reduces the chance of drug accumulation and may translate into an improved adverse effect profile. The drug has a bioavailability of 89% by the enteral route and effectively penetrates the inflamed rheumatoid synovium to achieve a concentration of approximately 50% of that seen in the plasma.[52,53] Animal studies have demonstrated almost complete metabolism with 30% biliary and 70% renal excretion. Hepatic metabolism is achieved, at least in part, by the cytochrome P450 system and it can be increased by enzyme inducers.[51]

In biological assays meloxicam has demonstrated the greatest COX-2 selectivity of the NSAIDs tested (table I).[28] Indeed, in a study using a rat pleurisy model, meloxicam was twice as potent as tenoxicam, 3 times as potent as flubriprofen, 8 times as potent as diclofenac, and 20 times as potent as tenidap at inhibition PGE_2 biosynthesis.[54]

Meloxicam has now been administered to more than 5000 patients predominantly with rheumatoid arthritis or osteoarthritis in clinical trials.[55] The most commonly used comparator drugs used in these trials were diclofenac, piroxicam and naproxen. At a dosage of up to 15 mg/day meloxicam has an efficacy equivalent to the comparative drugs with a trend in favour of improved gastrointestinal tolerability.[55] In the earliest stages of the drugs development doses up to 60 mg/day were used and these doses were not associated with increased gastrointestinal adverse effects.[55] This suggests that the conventional dose for meloxicam has a reasonable safety margin.

In the treatment of osteoarthritis meloxicam has been used in 5 major double blind trials involving about 1800 patients.[55-57] In these trials meloxicam demonstrated a clear superiority over placebo and an equivalent efficacy to comparator therapies. There was no significant difference in gastrointestinal adverse effects between therapies though the trend was in favour of meloxicam.

In the treatment of rheumatoid arthritis, controlled double blind studies over periods of 3 weeks to 6 months have demonstrated that the efficacy of meloxicam 7.5 mg/day and 15 mg/day is comparable to naproxen 750 mg/day[58] and piroxicam 20 mg/day, respectively.[59] In the 6 month comparison of meloxicam 7.5 mg/day (199 patients) with naproxen 750 mg/day (180)[58] there was no difference between the groups regarding the primary efficacy variables (global efficacy assessment by the patient and investigator, number of painful/tender and swollen joints). There were fewer gastrointestinal adverse effects in the meloxicam treated group (30%) compared with the naproxen-treated group (44%) and significantly more patients discontinued their therapy in the naproxen-treated group due to these adverse effects. In addition there were significant decreases in haemoglobin level and increases in serum creatinine and urea levels in the naproxen-treated group compared with the meloxicam group. However, the number of discontinuations due to lack of efficacy favoured the naproxen-treated group (26 patients) compared with the meloxicam-treated group (47).

In the 3-week comparison of meloxicam 15 mg/day (141 patients) with piroxicam 20 mg/day (135) there were no differences between the groups in terms of both efficacy and safety.[59] There was

a trend in favour of meloxicam with respect to gastrointestinal tolerance. There was no difference between the groups in terms of withdrawals due to lack of efficacy.

Overall, using data from all the above studies, the incidence of serious gastrointestinal events (perforation, ulcer and haemorrhage) was significantly lower in those patients taking meloxicam than diclofenac or piroxicam. For other body systems, meloxicam would appear to have a comparable safety profile to standard NSAIDs.[58-60]

In summary, meloxicam is a new NSAID which *in vitro* demonstrates high COX-2 selectivity. In the clinical trials thus far performed meloxicam appears to have an equivalent efficacy to standard NSAIDs combined with a lesser incidence of gastrointestinal adverse effects. The mechanism for this is not known but may relate to its COX-2 selectivity.

6. Conclusions

From the clinical data currently available it does seem that the COX selectivity of a NSAID is a significant determinant of the incidence of adverse effects. However, COX selectivity is not the whole story and other factors are also important. Currently, COX selectivity does not seem to be a clear determinant of clinical efficacy. It can be argued that of the currently available NSAIDs, nabumetone and etodolac have among the most favourable adverse effect profiles. Both of these drugs appear relatively COX-2 selective but have other important properties that contribute to their overall adverse effect profile. In initial studies, the new COX-2 selective inhibitor meloxicam, recently launched in its first market, has demonstrated clinical efficacy and a favourable gastrointestinal adverse effect profile.

Caution must remain about the potential of highly selective COX-2 inhibitors to affect normal physiological processes other than inflammation. It is interesting to note that mice genetically targeted to be deficient in COX-2 developed renal dysplasia (100% penetrance) and cardiac fibrosis (50% penetrance) but had normal inflammatory responses to standard models.[61] The conclusion to be drawn is that the complete implications of COX inhibition are not yet understood. However, meloxicam, the most selective COX-2 NSAID discussed, has not been associated with an excess of any renal toxicity.

COX-2 inhibition may interfere with the normal physiology of the uterus and embryonic membranes, although clinically this should not pose a problem as NSAIDs are normally avoided during pregnancy. The clinical significance of inducible COX-2 in prostaglandin signalling in the brain is not known, hence the significance of inhibition is not known either. In the vascular endothelium and skeletal muscle the inducible enzyme appears to have an important role in the response to injury or mechanical stress. Again the significance of inhibition of these functions is not clear. The full effects of COX-2 inhibition can probably only be determined with accurate postmarketing surveillance studies.

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